## BMI-1 suppresses contact inhibition and stabilizes YAP in Ewing sarcoma.

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**Public Summary:**
In the current study we have identified a previously unreported link between the polycomb group protein BMI-1, contact inhibition and the Hippo-YAP pathway. Our observation that continued high-level expression of YAP is necessary for Ewing sarcoma family tumors (ESFT) cell proliferation and anchorage-independent growth, implicate YAP as an important oncogene in ESFT and a potentially critical effector of BMI-1-mediated tumorigenicity. It will be interesting to learn if BMI-1-mediated stabilization of YAP and prevention of contact inhibition contribute to the pathogenesis of other human cancers and to the tumorigenicity and invasiveness of BMI-1-positive cancer stem cells.

**Scientific Abstract:**
The polycomb group family protein BMI-1 is overexpressed by and functions as an oncogene in many different human cancers. We have previously shown that BMI-1 promotes the tumorigenicity of Ewing sarcoma family tumors (ESFTs) and that this is mediated independently of CDKN2A repression. In this study, we have discovered that high levels of BMI-1 confer resistance to contact inhibition in ESFT cells. Using stable retroviral transduction, we evaluated the consequences of BMI-1 knockdown on the growth of CDKN2A wild-type and mutant ESFT cells in subconfluent and confluent conditions. Although knockdown of BMI-1 had no effect on proliferation in low-density cultures, at high cell densities it resulted in cell cycle arrest and death. The normal cell contact inhibition response is mediated, in large part, by the recently described Hippo pathway which functions to inhibit cell proliferation and promote cell death by inactivating the Yes-Associated Protein (YAP). Significantly, we found that YAP levels, activity and expression did not diminish in confluent ESFT cells that expressed high levels of BMI-1. In contrast, YAP expression and nuclear localization were reduced in confluent BMI-1 knockdown cells suggesting that silencing of BMI-1 restored contact inhibition by restoring normal activation of the Hippo-YAP growth-suppressor pathway. Importantly, knockdown of YAP in ESFT cells resulted in profound inhibition of cell proliferation and anchorage-independent colony formation suggesting that stabilization and continued expression of YAP is critical for ESFT growth and tumorigenicity. Together, these studies reveal a previously unrecognized link between BMI-1, contact inhibition and the Hippo-YAP pathway and suggest that resistance to contact inhibition in BMI-1 overexpressing cancer cells may be in part a result of Hippo inhibition and aberrant stabilization of YAP.Oncogene advance online publication, 20 December 2010; doi:10.1038/onc.2010.571.